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META-ANALYSIS

Pharmacologic Treatment of Heart Failure With Reduced Ejection Fraction

An Updated Systematic Review and Network Meta-Analysis

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ABSTRACT

BACKGROUND In 2022, a network meta-analysis showed that a combination of β-blockers, angiotensin receptor-neprilysin inhibitors (ARNi), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 inhibitors (SGLT2i) was most effective in reducing all-cause mortality in heart failure with reduced ejection fraction (HFrEF). This study updates the treatment benefit by including additional large randomized controlled trials (RCTs) since 2022, including the VICTOR (Vericiguat Global Study in Participants with Chronic Heart Failure) trial.

OBJECTIVES The goal of this study was to evaluate and compare regimens of pharmacotherapy in patients with HFrEF.

METHODS MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases were searched for RCTs in patients with HFrEF through April 2025. Using frequentist network meta-analysis, HRs for all-cause mortality (primary outcome), cardiovascular death, and the composite of cardiovascular death or heart failure hospitalization (secondary outcomes) were estimated. Absolute benefits were quantified as life-years gained by using BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure) and ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) cohort data.

RESULTS The analysis included 103,754 patients across 89 randomized controlled trials. Relative to placebo, quintuple therapy with ARNi, β-blockers, MRAs, SGLT2i, and vericiguat most effectively reduced all-cause mortality (HR: 0.35; 95% CI: 0.27-0.45), followed by quadruple therapy with ARNi, β-blockers, MRAs, and SGLT2i (HR: 0.39; 95% CI: 0.32-0.49). For a representative 70-year-old patient, quadruple therapy (ARNi/β-blockers/MRAs/SGLT2i) provided 5.3 additional life-years (95% CI: 2.8-7.7) vs no treatment, while quintuple therapy (ARNi/β-blockers/MRA/SGLT2i/vericiguat) provided 6.0 additional life-years (95% CI: 3.7-8.4).

CONCLUSIONS This analysis reinforces the substantial mortality and morbidity benefit associated with the currently recommended quadruple therapy regimen (ARNi, β-blockers, MRAs, and SGLT2i) in patients with HFrEF. The addition of vericiguat may provide an incremental survival gain of approximately 0.7 year beyond that achieved with quadruple therapy. However, these results should be regarded as exploratory, as they are derived from a secondary endpoint of a single trial. (JACC. 2025;86:2513-2526) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

ARNi = angiotensin receptor–neprilysin inhibitors

CV = cardiovascular

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

GLP-1 agonists = glucagon-like peptide-1 receptor agonist

MRA = mineralocorticoid receptor antagonist

NNT = number needed to treat

RCT = randomized controlled trial

SGLT2i = sodium-glucose cotransporter 2 inhibitor

Heart failure (HF) remains a significant source of mortality and morbidity globally.[1] Over the past 3 decades, landmark clinical trials have progressively expanded therapeutic options for patients with HF with reduced ejection fraction (HFrEF).[2,3]

The landscape of HFrEF treatment has undergone rapid evolution in recent years. Previous trials established angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor antagonists (MRAs) as foundational therapies. The introduction of angiotensin receptor–neprilysin inhibitors (ARNi)[4] and sodium-glucose cotransporter 2 inhibitors (SGLT2i)[4-6] established the foundational 4 therapies for HFrEF. Concurrently, novel agents targeting distinct pathophysiological pathways have emerged, including vericiguat (a soluble guanylyl cyclase stimulator)[7,8] and omecamtiv mecarbil (a cardiac myosin activator),[9] both of which have exhibited clinical efficacy in large-scale randomized controlled trials (RCTs).

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Previous network meta-analyses have shown that a combination of ARNi, β-blockers, MRAs, and SGLT2i is most effective in reducing all-cause mortality, cardiovascular (CV) death, and HF hospitalization.[10-16] However, additional large-scale RCTs have been published since these previous analyses, providing further evidence on the role of newer agents such as vericiguat.

Therefore, this updated systematic review and network meta-analysis extends our previous work[11] by incorporating the latest evidence published through April 2025 in patients with HFrEF. This analysis seeks to quantify the comparative effectiveness of current therapeutic combinations and estimate their aggregate impact on clinical outcomes and life expectancy, thereby informing evidence-based treatment decisions in contemporary clinical practice.[17]

METHODS

PROTOCOL AND STUDY DESIGN. A prespecified protocol and analysis plan was registered on PROSPERO (PROSPERO ID: CRD420251054997). Data were analyzed by using a frequentist statistical framework, and the results are reported following the Preferred Reporting Items for Systematic reviews and Meta-analyses extension statement for network meta-analyses.[17]

SEARCH STRATEGY, SELECTION CRITERIA, AND DATA EXTRACTION. We updated our previous systematic search of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials to include RCTs published between January 2021 and April 2025. The complete search strategy and protocol are available in the Supplemental Appendix and on PROSPERO.

Eligible studies included adult patients (aged ≥18 years) with HFrEF, defined as a left ventricular ejection fraction ≤50%. Studies were excluded in which the entire population had comorbidities likely to significantly affect outcomes (eg, post-myocardial infarction or studies exclusively enrolling patients with diabetes). Trials focused on acute HF or comparisons within a single drug class were also excluded.

Consistent with our previous review,[11] the pharmacologic agents of interest included: digoxin, hydralazine-isosorbide dinitrate, ACEI, ARBs, β-blockers, MRAs, ivabradine, ARNi, SGLT2i, vericiguat, and omecamtiv mecarbil. We additionally included studies evaluating glucagon-like peptide-1 receptor agonists (GLP-1 agonists) in patients with HFrEF. All studies published between 1987 and April 2025 were considered.

After removing duplicates, all titles and abstracts were independently screened by at least 2 of 6 investigators (B.J.v.E., D.C.H.C., G.N.T., F.M.H., T.-H. K.T., and A.K.) to identify potentially eligible studies. Full-text articles of selected records were then reviewed independently by 2 investigators (B.J.v.E. and D.C.H.C.). Any disagreements were resolved through consensus. The same 2 investigators conducted data extraction (B.J.v.E. and D.C.H.C.), and they cross-checked each other's entries to ensure the robustness of the data extraction process.

Data from the unpublished VICTOR (Vericiguat Global Study in Participants with Chronic Heart Failure; NCT05093933)[18] trial were provided by the trial sponsors prior to peer-reviewed publication. The

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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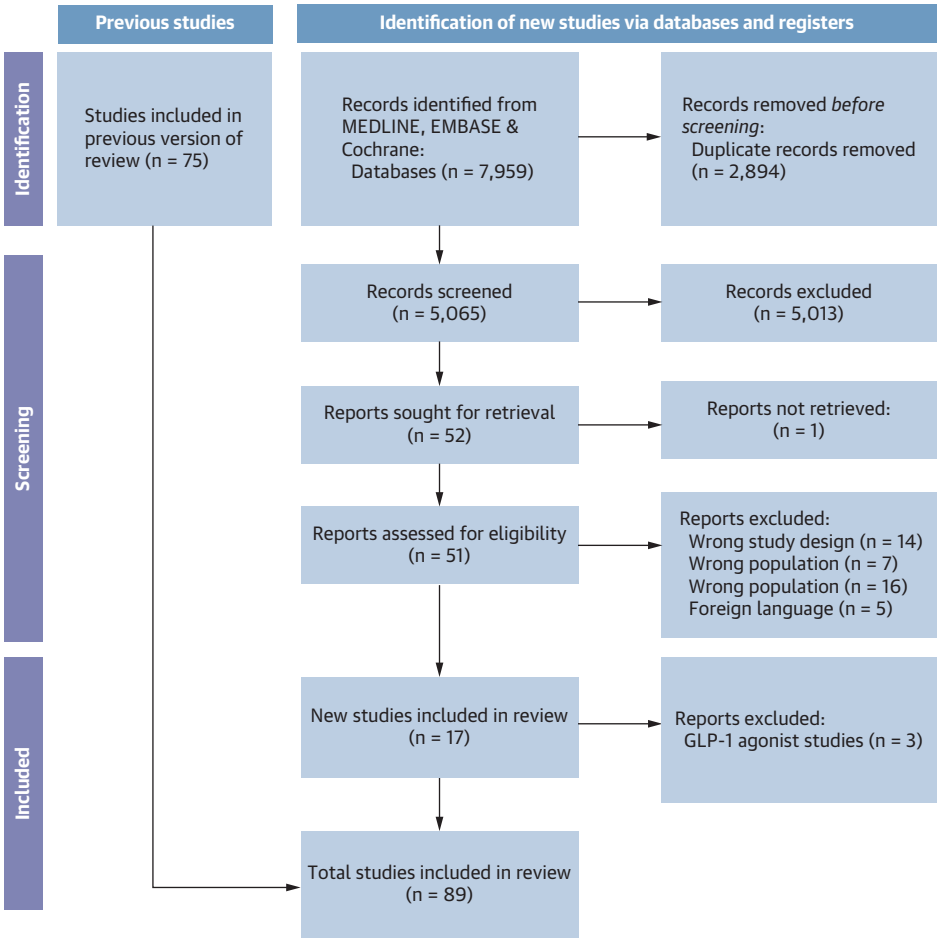
FIGURE 1 Study Selection Flowchart


Previous studies
Identification of new studies via databases and registers
Identification
Screening
Included
Studies included in previous version of review (n = 75)
Records identified from MEDLINE, EMBASE & Cochrane: Databases (n = 7,959)
Records removed *before screening*: Duplicate records removed (n = 2,894)
Records screened (n = 5,065)
Records excluded (n = 5,013)
Reports sought for retrieval (n = 52)
Reports not retrieved: (n = 1)
Reports assessed for eligibility (n = 51)
Reports excluded: Wrong study design (n = 14) Wrong population (n = 7) Wrong population (n = 16) Foreign language (n = 5)
New studies included in review (n = 17)
Reports excluded: GLP-1 agonist studies (n = 3)
Total studies included in review (n = 89)

Flow diagram showing the identification, screening, eligibility assessment, and inclusion of randomized controlled trials evaluating pharmacologic therapies in heart failure with reduced ejection fraction. The diagram outlines the number of records retrieved from databases, reasons for exclusion at each stage, and the final set of studies included in the network meta-analysis. GLP-1 agonist = glucagon-like peptide-1 receptor agonist.

sponsors had no role in the design of this network meta-analysis, its funding, or in the generation, analysis, or interpretation of the results presented herein.

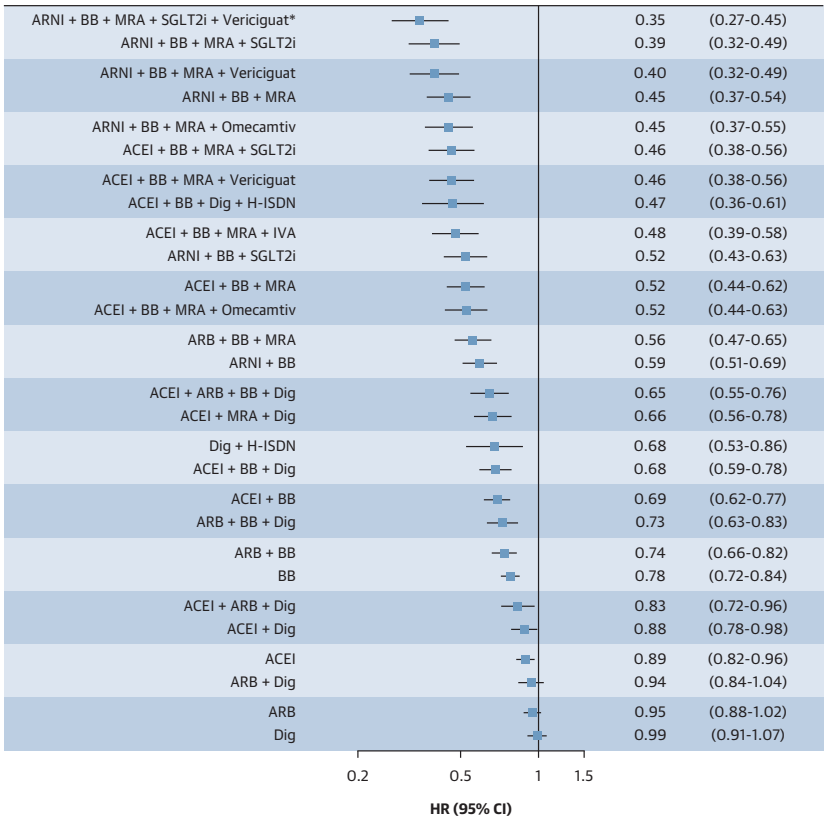
OUTCOMES. The primary outcome was all-cause mortality. Secondary outcomes included CV death and a composite of CV death or hospitalization for HF.

NETWORK META-ANALYSIS. The network meta-analysis was performed by using a frequentist statistical framework, which incorporates graph-theoretical approaches developed initially for electrical networks.[19-22] Both fixed-effects and random-effects models were constructed to assess treatment effects. Heterogeneity was assessed by using the I^2 and the τ^2 statistic with random-effects models applied when I^2 exceeded 30%. As an important secondary analysis, we explored potential temporal heterogeneity by conducting era-stratified analyses, evaluating all studies separately across 3 periods: pre-2000, 2000 to 2010, and post-2010.

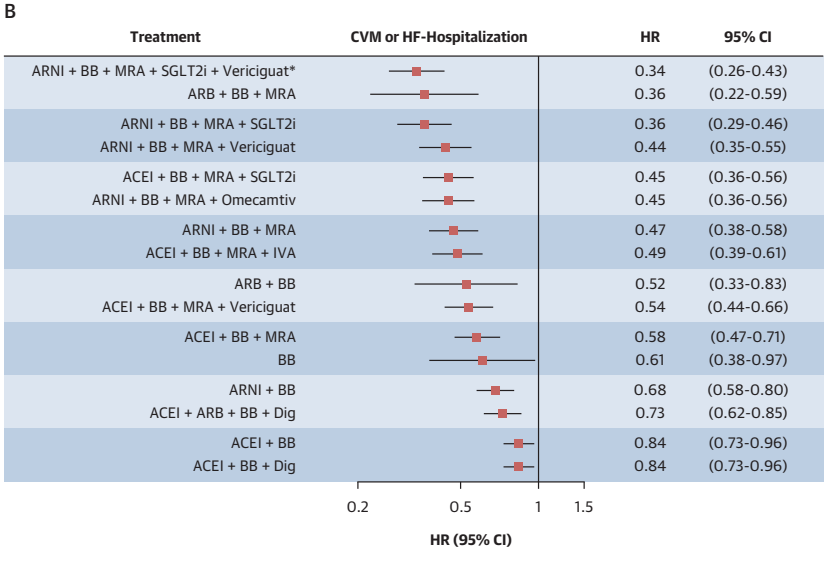
To evaluate the effect of treatments comprising multiple components (eg, ARNi, β-blockers, MRAs), an additive component network meta-analysis model was used. This model assumes that the combined effect of a treatment regimen equals the sum of its individual components. To test whether treatments were additive, an additive model assumptions test was performed for all outcomes.

FIGURE 2 Forest Plot of HRs for Treatment Regimens

A


Treatment
All-Cause Mortality
HR
95% CI
ARNI + BB + MRA + SGLT2i + Vericiguat* 0.35 (0.27-0.45)
ARNI + BB + MRA + SGLT2i 0.39 (0.32-0.49)
ARNI + BB + MRA + Vericiguat 0.40 (0.32-0.49)
ARNI + BB + MRA 0.45 (0.37-0.54)
ARNI + BB + MRA + Omecamtiv 0.45 (0.37-0.55)
ACEI + BB + MRA + SGLT2i 0.46 (0.38-0.56)
ACEI + BB + MRA + Vericiguat 0.46 (0.38-0.56)
ACEI + BB + Dig + H-ISDN 0.47 (0.36-0.61)
ACEI + BB + MRA + IVA 0.48 (0.39-0.58)
ARNI + BB + SGLT2i 0.52 (0.43-0.63)
ACEI + BB + MRA 0.52 (0.44-0.62)
ACEI + BB + MRA + Omecamtiv 0.52 (0.44-0.63)
ARB + BB + MRA 0.56 (0.47-0.65)
ARNI + BB 0.59 (0.51-0.69)
ACEI + ARB + BB + Dig 0.65 (0.55-0.76)
ACEI + MRA + Dig 0.66 (0.56-0.78)
Dig + H-ISDN 0.68 (0.53-0.86)
ACEI + BB + Dig 0.68 (0.59-0.78)
ACEI + BB 0.69 (0.62-0.77)
ARB + BB + Dig 0.73 (0.63-0.83)
ARB + BB 0.74 (0.66-0.82)
BB 0.78 (0.72-0.84)
ACEI + ARB + Dig 0.83 (0.72-0.96)
ACEI + Dig 0.88 (0.78-0.98)
ACEI 0.89 (0.82-0.96)
ARB + Dig 0.94 (0.84-1.04)
ARB 0.95 (0.88-1.02)
Dig 0.99 (0.91-1.07)
0.2
0.5
1
1.5
HR (95% CI)

B


Treatment
CVM or HF-Hospitalization
HR
95% CI
ARNI + BB + MRA + SGLT2i + Vericiguat* 0.34 (0.26-0.43)
ARB + BB + MRA 0.36 (0.22-0.59)
ARNI + BB + MRA + SGLT2i 0.36 (0.29-0.46)
ARNI + BB + MRA + Vericiguat 0.44 (0.35-0.55)
ACEI + BB + MRA + SGLT2i 0.45 (0.36-0.56)
ARNI + BB + MRA + Omecamtiv 0.45 (0.36-0.56)
ARNI + BB + MRA 0.47 (0.38-0.58)
ACEI + BB + MRA + IVA 0.49 (0.39-0.61)
ARB + BB 0.52 (0.33-0.83)
ACEI + BB + MRA + Vericiguat 0.54 (0.44-0.66)
ACEI + BB + MRA 0.58 (0.47-0.71)
BB 0.61 (0.38-0.97)
ARNI + BB 0.68 (0.58-0.80)
ACEI + ARB + BB + Dig 0.73 (0.62-0.85)
ACEI + BB 0.84 (0.73-0.96)
ACEI + BB + Dig 0.84 (0.73-0.96)
0.2
0.5
1
1.5
HR (95% CI)

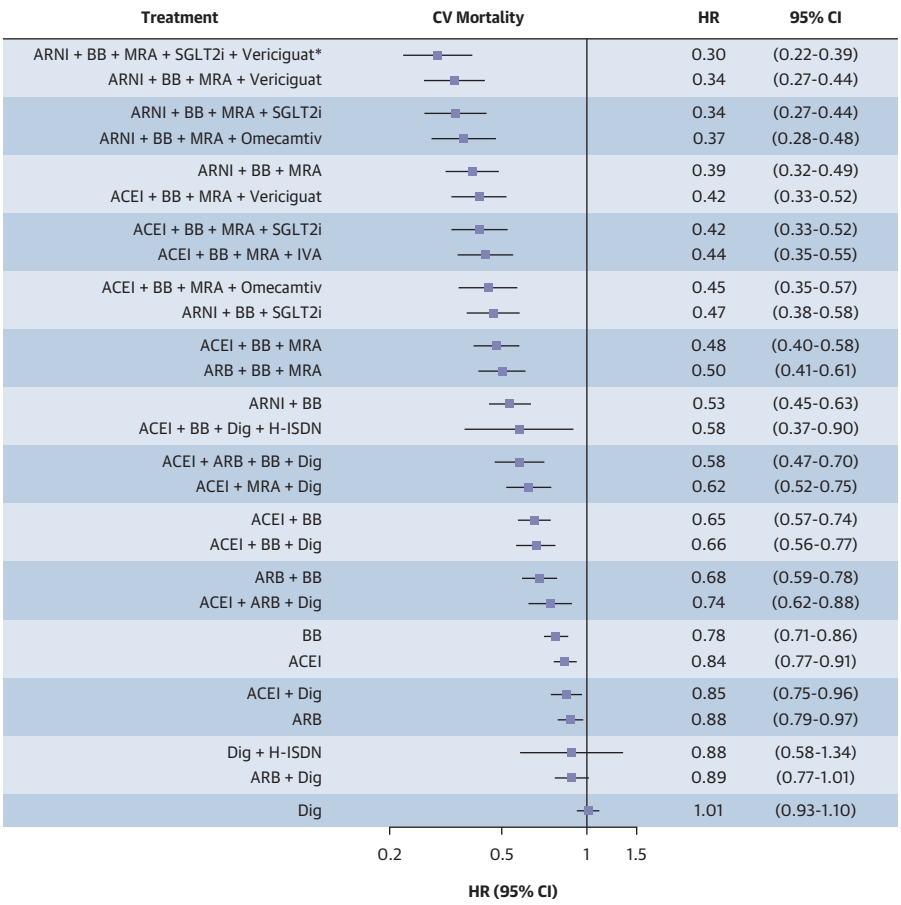
Continued on the next page

Comparisons were based on background therapies used within individual trials; thus, only treatment combinations that formed part of a connected network were analyzed.

Many earlier trials did not include composite endpoints such as CV death or hospitalization for HF. CIBIS (Cardiac Insufficiency Bisoprolol Study) III served as a reference for analyzing these composite

FIGURE 2 Continued

C



Forest plots summarizing the estimated HRs for all-cause mortality (A), cardiovascular mortality (B), and the composite of cardiovascular death or heart failure hospitalization (C) for all evaluated drug combinations in heart failure with reduced ejection fraction. Results are derived from the network meta-analysis, with placebo (PLBO) as the reference, and abbreviations are provided for each drug class. *The incremental benefit of quintuple therapy is exploratory and based on a single trial's secondary endpoint. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; BB = beta-blocker; Dig = digoxin; H-ISDN = hydralazine-isosorbide dinitrate; IVA = ivabradine; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter 2 inhibitors.

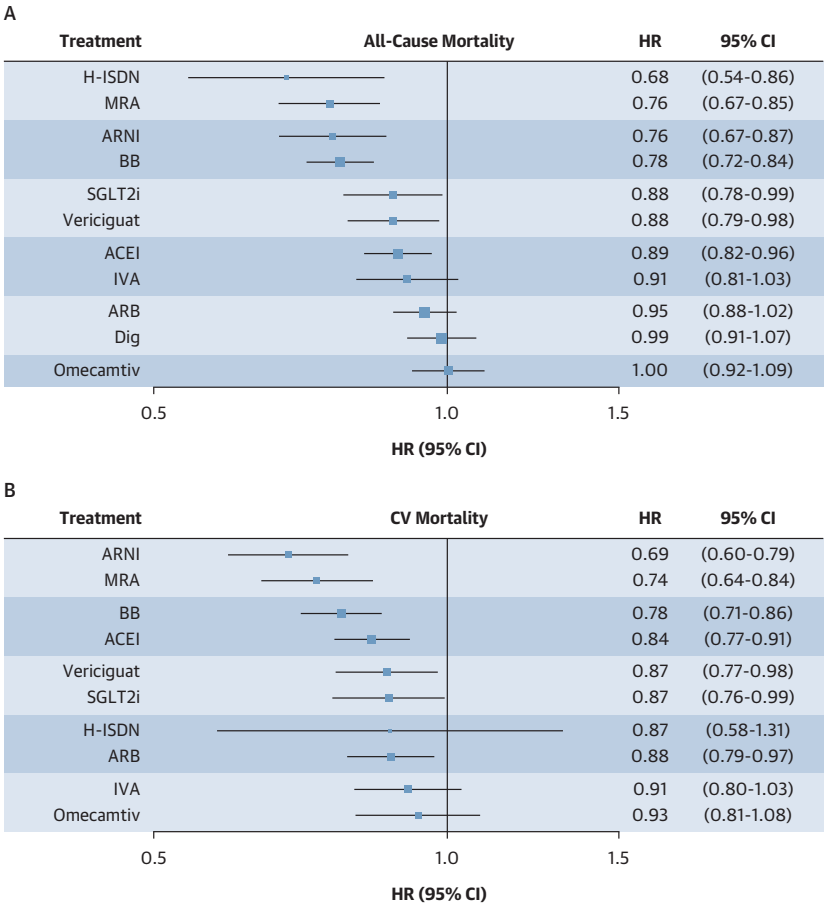
outcomes.[23] Patients were on background therapy if at least 50% of participants in the trial received the treatment.[11] Background therapy variations between studies were addressed through sensitivity analyses examining treatment effects across different patterns of concomitant medication use.

HRs for time-to-event outcomes are reported. Treatments were ranked by using P-scores.[24,25]

To assess confidence in the results, the CINeMA (Confidence in Network Meta-Analysis)[26] framework was applied. This framework evaluates 6 domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Within-study bias was assessed by using a modified Cochrane risk-of-bias tool across 6 criteria (eg, allocation concealment, blinding, missing data). A study was classified as high risk if it had >3 domains rated as high risk. Funnel plot symmetry and the Egger test were used to assess reporting bias.

Indirectness was considered low, in accordance with published guidelines and based on the similarity of study populations, interventions, and outcomes definitions across the included trials. All studies enrolled patients with HFrEF, used comparable pharmacologic interventions, and reported

FIGURE 3 Effects of Individual Drug Classes on Mortality

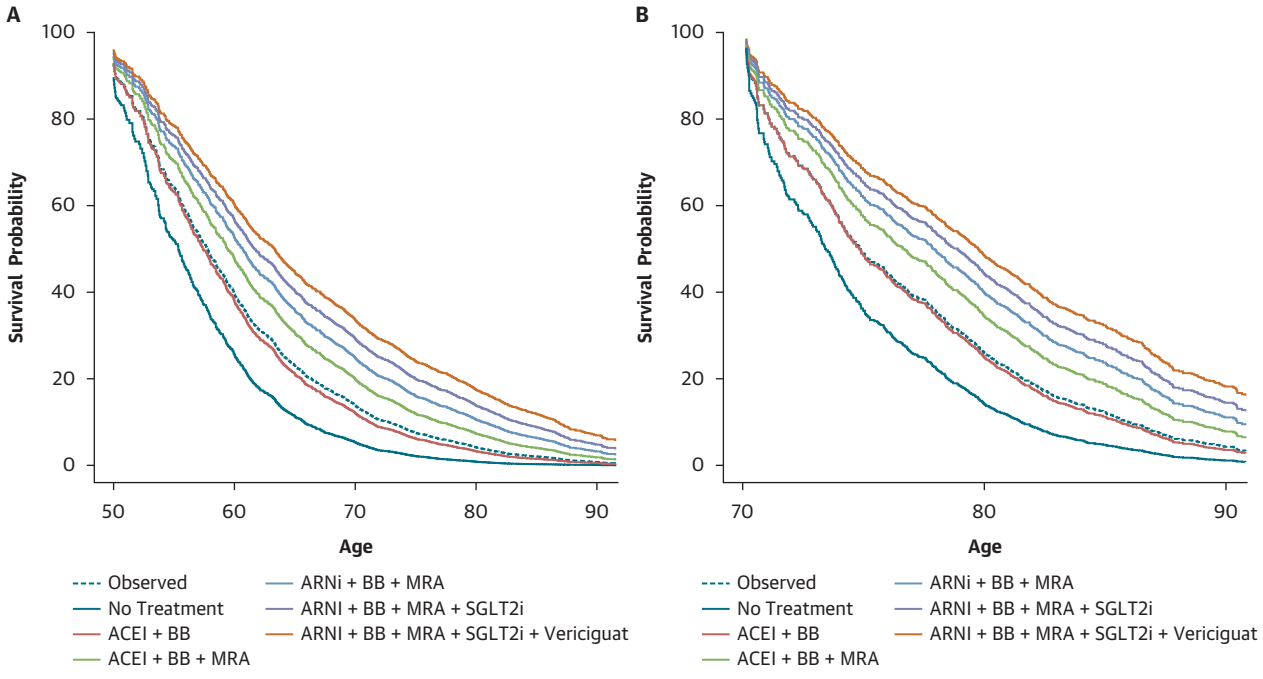


Forest plots showing the association between each pharmacologic class and all-cause mortality (A) and cardiovascular mortality in patients with heart failure with reduced ejection fraction (B) based on pooled HRs from the network meta-analysis. PLBO is used as the reference category, and abbreviations for drug classes are provided. Abbreviations as in Figure 1.

standardized clinical outcomes. Imprecision was assessed by comparing 95% CIs with a predefined equivalence range (OR: 2.0). This conservative threshold was selected to improve the robustness of estimates, in which advances in HF therapy have resulted in progressively more modest treatment effects compared with the conventional Grades of Recommendation, Assessment, Development, and Evaluation recommendation of OR = 2.5.[27] Incoherence (disagreement between direct and indirect evidence) was evaluated by using a global design-by-treatment interaction model.

The potential life-years gained were estimated in the BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure) and ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registries.[28-30] Actuarial (age-based) models were used to estimate life-years gained for different treatment combinations.[30] This method treats age as the time-to-event variable. Nonparametric Kaplan-Meier estimates were calculated for overall life expectancy at each year of age using a life-table approach based on the area under the survival curve. Because none of the study medications exhibited significant age interactions, the observed differences in survival curves represent predicted event-free survival and remaining life expectancy. Variations in baseline pharmacotherapy were addressed by calculating treatment effects for each therapeutic combination relative to the patient's existing regimen. For instance, when evaluating a patient receiving ACEIs and β-blockers, the projected

FIGURE 4 Survival Benefit at Age 50 Years and 70 Years



(A) Estimated life-years gained for a 50-year-old patient with heart failure with reduced ejection fraction receiving different pharmacologic regimens compared with PLBO. Estimates are derived from the network meta-analysis and survival modeling, illustrating the potential magnitude of benefit in a younger patient population. (B) Estimated life-years gained for a 70-year-old patient with heart failure with reduced ejection fraction receiving different pharmacologic regimens compared with PLBO. Estimates are derived from the network meta-analysis and survival modelling, illustrating the potential but comparatively smaller benefit in an older patient population. The incremental benefit of quintuple therapy is exploratory and based on a single trial's secondary endpoint. Abbreviations as in Figure 1.

life-years gained from adding ARNi, MRAs, and SGLT2i were calculated by using ACEIs and β-blockers as the reference standard. In addition, individual patient-level survival benefits were quantified by modeling the incremental advantage of various treatment combinations under the theoretical assumption of no prior therapy (ie, placebo). Number needed to treat (NNT) values were derived from estimated 2-year survival differences between each treatment regimen and placebo, with CIs calculated by using nonparametric bootstrap resampling.

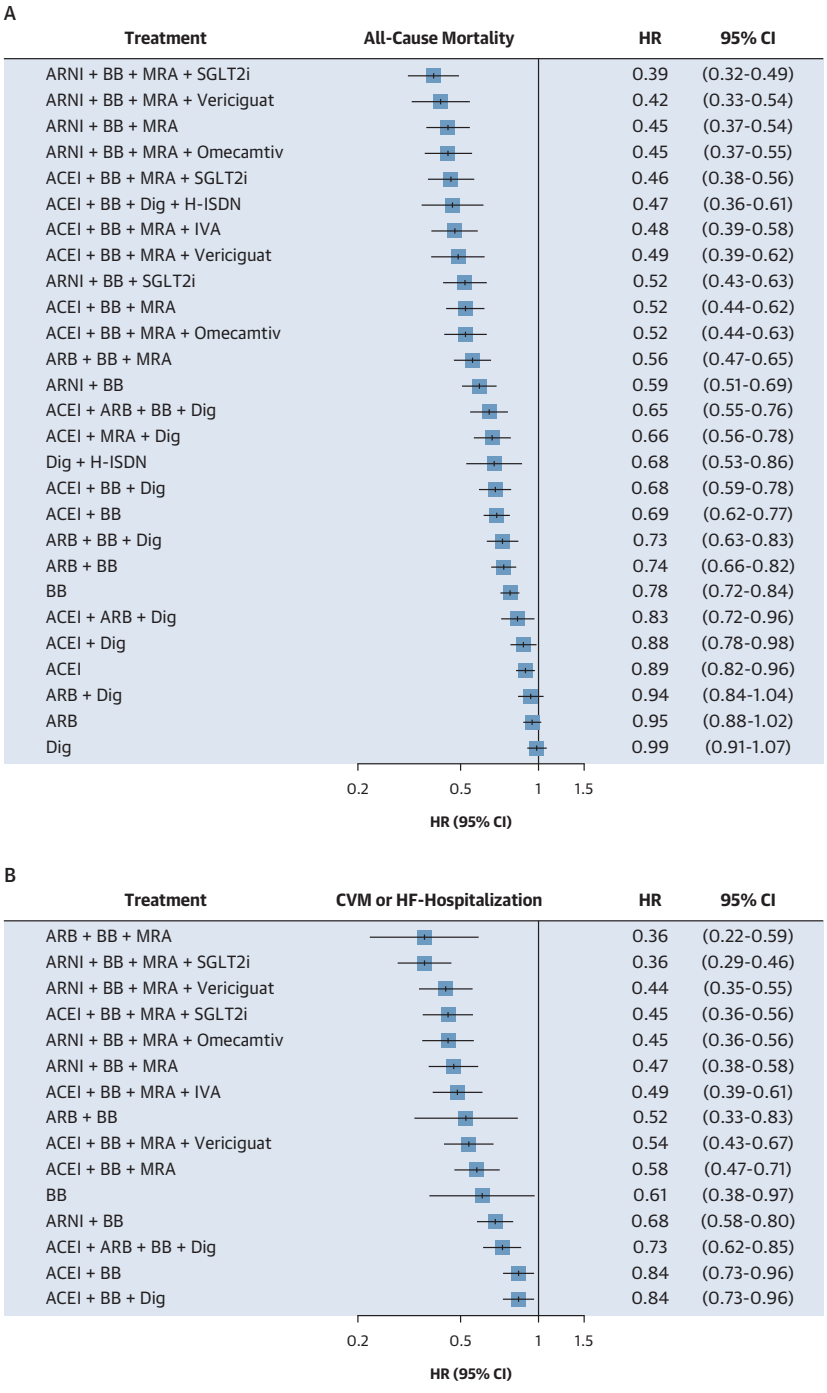
All statistical analyses were conducted by using the netmeta package in R version 4.0.2 (R Foundation for Statistical Computing). P values < 0.05 were considered statistically significant.

SENSITIVITY ANALYSES. A meta-regression was performed using all-cause mortality as the primary outcome to test the association between study year on treatment effect, as well as the association between age and treatment effect. In addition, a leave-one-out analysis was performed excluding the results of the VICTOR trial. A sensitivity analysis assuming 80% adherence after 2 years of treatment was conducted. In these analyses, treatment effects were adjusted for each patient's current therapy, with 20% of patients randomly assigned to remain on their existing treatment and not reach the target combination. A sensitivity analysis was additionally performed excluding A-HeFT (African-American Heart Failure Trial),[31] given its influence on the estimated effect sizes of the individual drugs. Last, in sensitivity analysis, we varied the threshold for background therapy from 50% to 70% and 90%.

RESULTS

STUDY IDENTIFICATION AND INCLUSION. The systematic search identified 5,065 additional entries. After screening titles and abstracts, 17 full-text articles met the eligibility criteria.[18,32-47] We identified only 3 articles using GLP-1 agonists, involving a total of 619 patients with only 36 mortality events, which we considered too few to provide meaningful estimates and were therefore excluded. In addition, data from the VICTOR trial were incorporated. Collectively, 89 studies were included for analysis (Figure 1),

FIGURE 5 Leave-One-Out Sensitivity Analysis Excluding the VICTOR Trial


A
Treatment
All-Cause Mortality
HR
95% CI
ARNI + BB + MRA + SGLT2i 0.39 (0.32-0.49)
ARNI + BB + MRA + Vericiguat 0.42 (0.33-0.54)
ARNI + BB + MRA 0.45 (0.37-0.54)
ARNI + BB + MRA + Omecamtiv 0.45 (0.37-0.55)
ACEI + BB + MRA + SGLT2i 0.46 (0.38-0.56)
ACEI + BB + Dig + H-ISDN 0.47 (0.36-0.61)
ACEI + BB + MRA + IVA 0.48 (0.39-0.58)
ACEI + BB + MRA + Vericiguat 0.49 (0.39-0.62)
ARNI + BB + SGLT2i 0.52 (0.43-0.63)
ACEI + BB + MRA 0.52 (0.44-0.62)
ACEI + BB + MRA + Omecamtiv 0.52 (0.44-0.63)
ARB + BB + MRA 0.56 (0.47-0.65)
ARNI + BB 0.59 (0.51-0.69)
ACEI + ARB + BB + Dig 0.65 (0.55-0.76)
ACEI + MRA + Dig 0.66 (0.56-0.78)
Dig + H-ISDN 0.68 (0.53-0.86)
ACEI + BB + Dig 0.68 (0.59-0.78)
ACEI + BB 0.69 (0.62-0.77)
ARB + BB + Dig 0.73 (0.63-0.83)
ARB + BB 0.74 (0.66-0.82)
BB 0.78 (0.72-0.84)
ACEI + ARB + Dig 0.83 (0.72-0.96)
ACEI + Dig 0.88 (0.78-0.98)
ACEI 0.89 (0.82-0.96)
ARB + Dig 0.94 (0.84-1.04)
ARB 0.95 (0.88-1.02)
Dig 0.99 (0.91-1.07)
0.2
0.5
1
1.5
HR (95% CI)
B
Treatment
CVM or HF-Hospitalization
HR
95% CI
ARB + BB + MRA 0.36 (0.22-0.59)
ARNI + BB + MRA + SGLT2i 0.36 (0.29-0.46)
ARNI + BB + MRA + Vericiguat 0.44 (0.35-0.55)
ACEI + BB + MRA + SGLT2i 0.45 (0.36-0.56)
ARNI + BB + MRA + Omecamtiv 0.45 (0.36-0.56)
ARNI + BB + MRA 0.47 (0.38-0.58)
ACEI + BB + MRA + IVA 0.49 (0.39-0.61)
ARB + BB 0.52 (0.33-0.83)
ACEI + BB + MRA + Vericiguat 0.54 (0.43-0.67)
ACEI + BB + MRA 0.58 (0.47-0.71)
BB 0.61 (0.38-0.97)
ARNI + BB 0.68 (0.58-0.80)
ACEI + ARB + BB + Dig 0.73 (0.62-0.85)
ACEI + BB 0.84 (0.73-0.96)
ACEI + BB + Dig 0.84 (0.73-0.96)
0.2
0.5
1
1.5
HR (95% CI)

Graphic displays the results of the leave-one-out sensitivity analysis excluding the VICTOR trial. Shown are the estimated HRs and 95% CIs for all-cause mortality (A), cardiovascular mortality (B), and the composite of cardiovascular mortality and heart failure hospitalization (C).

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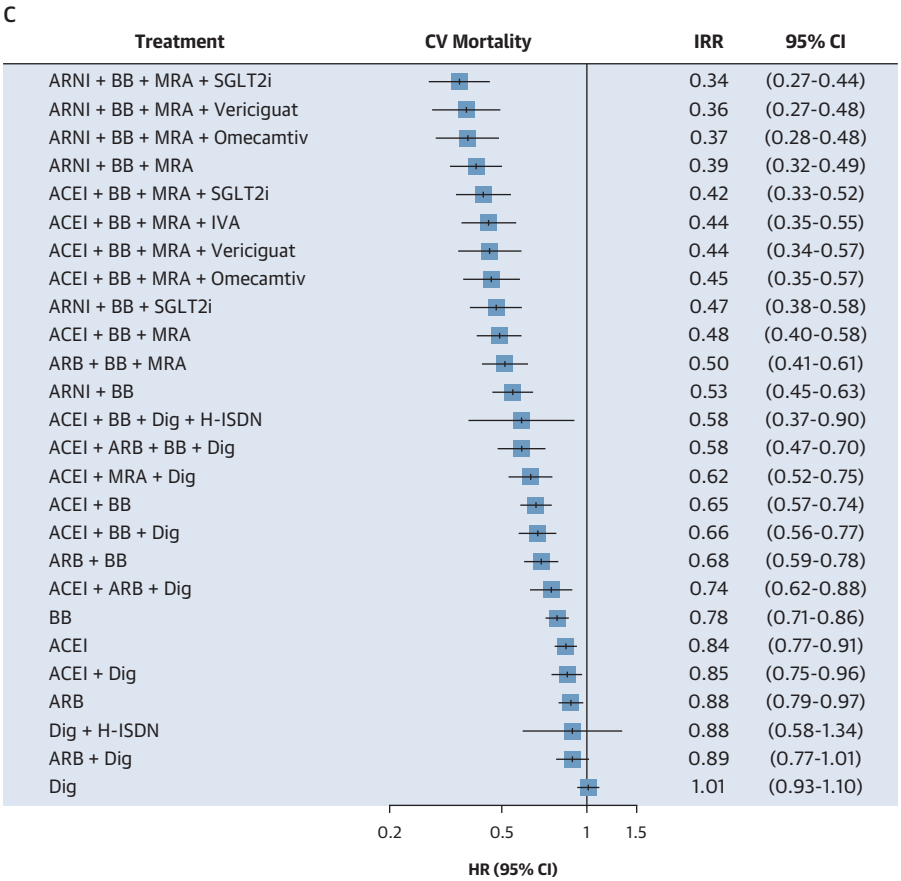
FIGURE 5 Continued



representing 103,754 patients with a cumulative follow-up of 199,724 patient-years. In total, 17 studies had <100 participants, while 24 studies included >1,000 participants. The median follow-up duration across studies was 9 months (Q1-Q3: 5.5-18.4 months). Baseline age (Supplemental Figure 1) and left ventricular ejection fraction were largely consistent across studies (Supplemental Figure 2).

BIAS ASSESSMENT AND PUBLICATION BIAS. The overall risk of bias was low (Supplemental Figure 3). The primary source of bias was a lack of blinding and reporting bias (Supplemental Table 1). There was no significant evidence of reporting bias based on the Egger test: mortality ($P = 0.072$), CV death and HF hospitalization composite ($P = 0.705$), or CV death alone ($P = 0.177$) (Supplemental Figure 4). Indirectness was considered low. Most comparisons did not show imprecision (Supplemental Table 2). Heterogeneity estimates were low to moderate: $I^2 = 0\%$ (range 0.0%-27.4%; $P = 0.688$) for all-cause mortality, 10.5% (range 0.0%-49.8%; $P = 0.342$) for the composite of CV death or HF hospitalization, and 3.1% (range 0.0%-28.7%; $P = 0.412$) for CV mortality. The τ^2 estimates were 0 for all-cause mortality, 0.0013 for CV mortality or HF hospitalization, and 0.0012 for CV mortality. No evidence of incoherence was found ($P > 0.10$). Confidence ratings were primarily high or moderate. The additive model assumptions test was nonsignificant for all outcomes ($P > 0.5$ for all). Observed vs predicted effects and additive model assumption tests for all outcomes are provided in Supplemental Tables 5 to 10.

OUTCOMES. All-cause mortality was reported in 84 studies with 102,489 patients and 18,520 deaths (Supplemental Table 3). The HR for all-cause mortality of the quintuple combination of ARNi, β-blockers, MRAs, SGLT2i, and vericiguat vs placebo was 0.35 (95% CI: 0.27-0.45). For the quadruple combination of ARNi, β-blockers, MRAs, and SGLT2i, the HR was 0.39 (95% CI: 0.32-0.49) (**Figure 2A**). Supplemental Table 4 ranks treatment regimens by

using surface under the cumulative ranking curve *P* values, and the network is shown in Supplemental Figures 5 and 6. Comparisons between combinations showed that the quintuple combination of ARNi, β-blockers, MRAs, SGLT2i, and vericiguat was associated with a significantly lower hazard for all-cause mortality compared with the quadruple combination of ARNi, β-blockers, MRAs, and SGLT2i (HR: 0.88; 95% CI: 0.79-0.98) (Supplemental Table 11). The association between individual treatments and all-cause mortality showed that hydralazine-isosorbide dinitrate was associated with the lowest risk of all-cause mortality (HR: 0.68; 95% CI: 0.54-0.86), followed by MRAs (HR: 0.76; 95% CI: 0.67-0.85) and ARNi (HR: 0.76; 95% CI: 0.67-0.87) (**Figure 3A**).

Among the included studies, 21 assessed the composite endpoint of CV death or HF hospitalization. The HR for the quintuple therapy of ARNi, β-blockers, MRAs, SGLT2i, and vericiguat for the composite outcome of CV mortality or HF hospitalization was 0.34 (95% CI: 0.26-0.43), followed by the combination of ARBs, β-blockers, and MRAs (HR: 0.36; 95% CI: 0.22-0.59) and ARNi, β-blockers, MRAs, and SGLT2i (HR: 0.36; 95% CI: 0.29-0.46) (**Figure 2B**). There was no significant difference between the combination of ARNi, β-blockers, MRAs, SGLT2i, and vericiguat vs ARNi, β-blockers, MRAs, and SGLT2i (HR: 0.93; 95% CI: 0.85-1.02) (Supplemental Table 12).

Among the included studies, 55 reported CV death as a standalone outcome. The HR of the quintuple combination was 0.30 (95% CI: 0.22-0.39). For the quadruple combination of ARNi, β-blockers, MRAs, and SGLT2i, the HR was 0.34 (95% CI: 0.27-0.44) (**Figure 2C**), and for the quadruple combination of ARNi, β-blockers, MRAs, and vericiguat, the HR was 0.34 (95% CI: 0.27-0.44). The quintuple combination of ARNi, β-blockers, MRAs, SGLT2i, and vericiguat was associated with a significantly lower hazard of CV mortality compared with the quadruple combination of ARNi, β-blockers, MRAs, and SGLT2i (HR: 0.87; 95% CI: 0.77-0.98) and compared with the quadruple combination of ARNi, β-blockers, MRAs, and vericiguat (HR: 0.87; 95% CI: 0.76-0.99) (Supplemental Table 13).

The association between individual treatments and CV mortality found that ARNi was associated with the lowest risk of CV mortality (HR: 0.69; 95% CI: 0.60-0.79), followed by MRAs (HR: 0.74; 95% CI: 0.64-0.84) and β-blockers (HR: 0.78; 95% CI: 0.71-0.86) (**Figure 3B**). Network plots for all outcomes are provided in Supplemental Figures 6 to 8.

SECONDARY ANALYSIS. Supplemental Figures 9 to 11 present the era-stratified analyses. The heterogeneity among the eras was low (pre-2000, I^2 = 2.9%, $\tau 2$ = 0.002; 2000-2010, maximum I^2 = 22.2%, $\tau 2$ = 0.008; post-2010, I^2 = 0%, $\tau 2$ = 0). In the contemporary era, the HR for all-cause mortality of treatment with quintuple therapy was 0.53 (95% CI: 0.41-0.69); for the quadruple therapy, this was 0.60 (95% CI: 0.47-0.77).

ESTIMATED LIFE-YEARS GAINED AND NNT. Survival modeling was performed in 7,376 patients from the BIOSTAT-CHF and ASIAN-HF trials, which included patients treated with ACEIs and β-blockers. Median age was 63 years (Q1-Q3: 54-72 years), with 1,664 (23%) women and 2,904 (43%) in NYHA functional class III/IV. Over a median follow-up of 22 months (Q1-Q3: 12-25 months), 1,287 (19%) participants died.

At baseline, 5,691 (77%) patients were taking ACEIs/ARBs, 6,018 (82%) were taking β-blockers, and 4,093 (55%) were taking MRAs. Compared with no treatment, the quintuple regimen of ARNi, β-blockers, MRAs, SGLT2i, and vericiguat increased life expectancy by 9.2 life-years (95% CI: 6.0-12.4) in 50-year-old patients and 6.0 life-years (95% CI: 3.7-8.4) in 70-year-old patients (Supplemental Table 14). Compared with no treatment, the quadruple regimen of ARNi, β-blockers, MRAs, and SGLT2i increased life expectancy by 7.8 life-years (95% CI: 4.6-11.1) in 50-year-old patients and 5.3 life-years (95% CI: 2.8-7.7) in 70-year-old patients. Similar trends were observed between the BIOSTAT-CHF and ASIAN-HF cohorts (**Figure 4**). When evaluating a scenario in which drug adherence was 80% after 2 years, the quintuple combination of ARNi, β-blockers, MRAs, SGLT2i, and vericiguat increased life-expectancy by 5.9 life-years (95% CI: 2.54-9.19) for a 50-year-old and 2.67 life-years (95% CI: 0.1-5.2) for a 70-year-old (Supplemental Table 15). The NNT for ARNi + β-blockers + MRAs + SGLT2i was 6.3 (95% CI: 6.2-6.4), and for the quintuple combination adding vericiguat it was 5.8 (95% CI: 5.8-5.9). Complete NNT results are provided in Supplemental Table 16.

SENSITIVITY ANALYSES. When excluding VICTOR, the quadruple regimen of ARNi, β-blockers, MRAs, and SGLT2i was found to be associated with the lowest risk of all-cause mortality (HR: 0.36; 95% CI: 0.29-0.46) (**Figure 5**, Supplemental Figures 12 to 14).

In sensitivity analyses using higher background therapy thresholds (the 70% threshold), the quadruple combination of ARNi, β-blockers, MRAs, and SGLT2i displayed the most significant mortality benefit (HR: 0.39; 95% CI: 0.32-0.49), followed closely by the combination of ARNi, β-blockers, MRAs, and vericiguat (HR: 0.42; 95% CI: 0.33-0.54).

When the threshold was increased to 90%, 2 triple-drug combinations showed equivalent efficacy:

ARNi, β-blockers, and MRAs (HR: 0.47; 95% CI: 0.39-0.56) and ARNi, β-blockers, and vericiguat (HR: 0.47; 95% CI: 0.39-0.57) (Supplemental Figures 15 to 20). A meta-regression did not find any association between study year and treatment effect (estimate = 0.0022 ± 0.0032; P = 0.487) or between age and treatment effect (estimate = 0.0006 ± 0.007 P = 0.941).

Results for the individual drugs are presented in Supplemental Figure 21, which displays the estimated effect sizes after exclusion of the A-HeFT trial. Hydralazine-isosorbide dinitrate remained the drug associated with the largest reduction in all-cause mortality (HR: 0.72; 95% CI: 0.55-0.95).

DISCUSSION

Results from this updated network meta-analysis confirm the robust evidence for the mortality and morbidity benefit of the currently recommended quadruple therapy regimen (ARNi, β-blockers, MRAs, and SGLT2i) in patients with HFrEF. The results also confirm that addition of vericiguat may confer a modest incremental survival benefit. The addition of vericiguat has the possibility of adding an extra 0.7 year beyond quadruple therapy; however, this finding is exploratory and derived from a secondary endpoint of a single trial.

The current analysis represents the most comprehensive evaluation of contemporary HFrEF pharmacotherapy to date, incorporating data from 89 RCTs and >103,000 patients. Importantly, our findings are consistent with and extend previous network meta-analyses while adding substantial new evidence.[10-16] Previous analyses were limited by the nascent adoption of therapy with SGLT2i. Our updated network incorporates new evidence from trials conducted during widespread use of SGLT2i, enabling more precise estimates of additive therapeutic benefits across contemporary treatment paradigms. These findings further strengthen the evidence supporting the incorporation of SGLT2i into the currently recommended quadruple therapy regimen. The inclusion of the VICTOR trial data, which enrolled the highest proportion of patients receiving comprehensive background therapy including SGLT2i, provides important additional insights into the effects of vericiguat in patients with HFrEF.

In the previously published VICTORIA (Vericiguat Global Study in Patients with Heart Failure with Reduced Ejection Fraction) trial,[7] vericiguat exhibited a modest reduction in the composite endpoint of CV death or hospitalization for HF among patients with high-risk HF. The VICTOR trial randomized approximately 6,000 stable ambulatory patients without a recent HF hospitalization or intravenous diuretic use to receive vericiguat or placebo added to contemporary guideline-directed therapy. Vericiguat did not significantly reduce the primary composite endpoint of CV death or hospitalization for HF. However, both all-cause mortality and CV mortality were lower in the vericiguat group. Accordingly, the finding from the current network meta-analysis that the addition of vericiguat may confer a modest incremental survival benefit on top of quadruple therapy is based on a secondary endpoint from a single trial and should therefore be interpreted with caution. The pooled analysis of the VICTOR and VICTORIA trials[48] suggests that the beneficial effects of vericiguat may be most pronounced in patients with N-terminal pro-B-type natriuretic peptide levels ≤6,000 pg/mL, highlighting the importance of careful patient selection. Importantly, clinical implementation might face significant challenges, including increased pill burden, potential adherence issues, and complex monitoring requirements that may limit real-world effectiveness. In addition, higher costs compared with most of the therapies from the quadruple treatment regimen that ran out of patent might limit availability in parts of the world. Further research is needed to assess the optimal sequence of up-titration and to evaluate clinical feasibility and the potential risk of discontinuation associated with the simultaneous use of multiple therapies.

The current analyses showed that quadruple therapy was associated with 5.3 life-years gained, compared with no therapy, in a 70-year-old patient. New evidence from trials conducted during widespread use of SGLT2i resulted in an even more robust estimation compared with the previous network meta-analysis. These findings extend prior cross-trial analyses, which have shown substantial survival benefits from comprehensive disease-modifying therapy.[11,49] Vaduganathan et al[49] used indirect comparisons across EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms), PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) to estimate that quadruple therapy could extend survival by 1.4 to 6.3 years relative to conventional treatment with ACEIs/ARBs and β-blockers, depending on patient age.

The addition of vericiguat may provide an incremental survival gain of approximately 0.7 years beyond that achieved with quadruple therapy. However, these results should be regarded as

exploratory, as they are derived from a secondary endpoint of a single trial. The differential benefit by age strata, with attenuated effects in older patients, likely reflects competing non-CV mortality and highlights the importance of considering life expectancy when implementing intensive multidrug regimens. Patient-centered outcomes such as event-free survival, years may provide valuable complementary information for clinical decision-making. Similarly, our previous network meta-analysis of 75 trials found that ARNi, β-blockers, MRAs, and SGLT2i provided 5.0 life-years gained in a 70-year-old patient compared with no treatment.[11]

STUDY LIMITATIONS. First, some degree of disagreement between direct and indirect evidence may remain undetected, particularly in less well-connected parts of the network in which fewer trials provide comparisons between specific treatment combinations. Although our global inconsistency tests did not reveal significant incoherence, localized inconsistencies may still exist that could affect the precision of estimates for specific comparisons. Second, the exclusion of 3 small GLP-1 agonist trials due to network connectivity constraints and imprecise estimates represents a limitation, although these emerging therapies may warrant separate systematic evaluation as the evidence base expands. Third, real-world applicability and generalizability may differ substantially from trial-based estimates. Trial populations often include highly selected populations and may vary from broader clinical populations in terms of comorbidities, medication adherence, health care access, and concurrent treatments. Fourth, the calculations here for life-years gained assume sustained adherence to treatment over time, which may not fully reflect real-world patterns. Treatment discontinuation rates vary considerably across drug classes and patient populations, and declining adherence over time could diminish the projected survival benefits. To account for this, we also modeled a reduced-adherence scenario, which yielded consistent conclusions regarding the relative treatment effects. Fifth, the substantial period over which the trials were conducted (1987-2025) may have introduced temporal bias. Changes in background medical therapy, diagnostic criteria, clinical care standards, and patient populations over nearly 4 decades could affect the consistency of treatment effects across studies. However, temporal analyses did not identify substantial heterogeneity. Finally, the quintuple therapy node is based on a single RCT (VICTOR), which limits the robustness of these conclusions despite favorable effect estimates and narrow CIs. Consequently, the evidence supporting the quintuple therapy node is derived from a single RCT, which may limit the robustness of the conclusion and stress the need for additional trials with high rates of background therapy.

CONCLUSIONS

In patients with HFrEF, treatment with the quadruple combination of ARNi, β-blockers, MRAs, and SGLT2i is associated with mortality and morbidity benefit. The addition of vericiguat may confer a modest incremental survival benefit. The addition of vericiguat may provide an incremental survival gain of approximately 0.7 years beyond that achieved with quadruple therapy. However, these results should be regarded as exploratory, as they are derived from a secondary endpoint of a single trial.

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APPENDIX For a supplemental appendix, figures, and tables, please see the online version of this paper.

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